**2650-Pos Board B80**
**Co-Aggregation of Alpha-Synuclein with Amylin(HIAPP) Leads to an Increased Risk in Type ii Diabetes Patients for Developing Parkinson's Disease**
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Clinical studies have reported that Type II diabetes patients (T2D) are more likely to develop Parkinson's disease (PD). However, the mechanisms which link these two diseases have remained elusive. In T2D, Amylin forms aggregates in the pancreas. However, it can also form neurotoxic oligomers in the brain. In PD, α-synuclein also forms neurotoxic amyloid aggregates. This work hypothesizes a new mechanism in which Amylin and α-synuclein may co-aggregate together and thus patients with T2D have an increased risk to develop PD. Since the non-amyloidogenic component (NAC) domain plays a major role in α-synuclein aggregation, we investigated the co-aggregation of Amylin-NAC oligomers.
In this study, we have constructed four different Amylin oligomeric structures and one NAC oligomeric structure, based on solid state NMR (ssNMR). We then constructed 12 Amylin-NAC oligomeric complexes while taking into consideration both single and double layered conformations. We then applied molecular dynamics simulations to investigate the stability of these structures. Our study has revealed three conclusions: 1) Amylin-NAC oligomers demonstrate polymorphic states with a preference towards two of the four Amylin oligomeric structures that co-aggregate with NAC.; 2) The Amylin-NAC oligomers' interactions at an atomistic level have been identified for the first time; 3) Amylin prefers to form single layer conformations with NAC over double layered conformations.

**2651-Pos Board B81**
**Insight into the Metal Binding Sites in Amylin Aggregates**
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Amylin peptide consists of 37 residues. The aggregation of Amylin is one of the symptoms of type 2 diabetes (T2D). Amylin's oligomers that are toxic lead to β-cells death and thus to decreasing of insulin's release to the blood and to progressing of T2D. The factors that affect Amylin aggregation are elusive, however it is known that Amylin peptides are found with insulin and zinc ions in the pancreatic β-cells and that zinc ions bind to Amylin oligomers and may inhibit Amylin aggregation. So far, it is unknown how zinc ions bind Amylin oligomers at the atomic resolution. Understanding the mechanism of zinc-binding sites in amylin oligomers is important for effective drug design to prevent and alleviate aggregation. We constructed Amylin oligomers based on ssNMR and x-ray crystallography. These experimental studies illustrate four different Amylin oligomeric models, which differ in the orientation of His18 in accordance of the core domain of Amylin. Other ssNMR study proposed that the binding site of zinc ions is His18. We applied molecular dynamics simulations to examine our constructed models. Two main conclusions had been obtained from our simulations. First, the binding site of zinc in Amylin is His18 which is located outside the core domain. Second, the zinc:Amylin ratio is 1:2.

**2652-Pos Board B82**
**Characterizing Kinetic Intermediate in Amyloid Self-Assembly**
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Amyloid self-assembly is tightly associated with protein misfolding diseases such as Alzheimer's disease, but the pathway of self-assembly as well as the genesis of amyloid polymorphism remains unclear. Combining isotope-edited IR and solid state NMR, we experimentally demonstrated that the nucleating core of Dutch mutant, Aβ (16-22) E22Q or Ac-16KLVFFA22Q-NH2 assembles into a kinetic intermediate of anti-parallel β-sheet that later transition automatically into parallel arrays as thermodynamically stable conformation. Additionally, we developed a method of quantifying such transition using IR spectroscopy. Our findings reveal that the process of amyloid self-assembly is subject to both kinetic and thermodynamic control and that the actually mechanism of self-assembly could be far more complicated than currently expected.

**2653-Pos Board B83**
**Site-Specific Structural Changes in Unmodified and Pyroglutamylated Amyloid Beta Peptide by Isotope-Edited Ftir**
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Amyloid beta-peptide (Abeta) forms cytotoxic assemblies that contribute to Alzheimer's disease. Recent evidence indicates that prefibrillar aggregates and not the fibrillar deposits exert the main toxic effect. In addition, naturally occurring N-terminally truncated and pyroglutamylated peptide (pE-Abeta) displays augmented cytotoxicity by an unknown mechanism. This study examines the conformational changes in both unmodified Abeta and pE-Abeta upon exposure to an aqueous environment. FTIR and circular dichroism were used to identify alpha-helix-to-beta-sheet conformational transitions of both peptides during aggregation. To gain site-specific structural information, the peptides were 13C,15N-labeled at residues 16-18 (KLV) or 36-39 (VGGV), followed by FTIR analysis. The peptides dried from hexafluoroisopropanol were alpha-helical (amide I peak at 1660-1657 cm-1) and showed negligible intensity of the labeled segments around 1615 cm-1, suggesting that in alpha-helical conformation the labeled amide groups behave like isolated oscillators. Upon addition of aqueous buffer (pH 7.2) both peptides rapidly adopted beta-sheet structure (amide I peak at 1637-1629 cm-1), with disproportionally prominent components around 1604-1597 cm-1 generated by the labeled segments. The intensity and the frequency of the amide I mode of the isotope-labeled segments suggest 12C-13C vibrational coupling, consistent with formation of anti-parallel beta-sheet structures. Moreover, the amide I contours of the peptides under near-physiological and low ionic strength conditions were significantly different; both peptides exhibited an increased alpha-helical and decreased beta-sheet propensity under low ionic strength conditions, indicating a strong influence of the ionic strength on the aggregation kinetics and accompanying structural changes. Ongoing studies focus on structural differences between the unmodified Abeta and pE-Abeta peptides as well as their mutual structural effects when combined at various molar ratios, in an attempt to understand the structural basis of the elevated cytotoxicity of pE-Abeta.

**2654-Pos Board B84**
**Preparation Protocols of Beta-Amyloid (1-40) Promote the Formation of Polymorphic Aggregates and Altered Interactions with Lipid Bilayers**
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The appearance of neuritic amyloid plaques comprised of β-amyloid peptide (Aβ) in the brain is a predominant feature in Alzheimer's disease (AD). In the aggregation process, Aβ samples a variety of potentially toxic aggregate species, ranging from small oligomers to fibrils. Aβ has the ability to form a variety of morphologically distinct and stable amyloid fibrils. Commonly referred to as polymorphs, such distinct aggregate species may play a role in variations of AD pathology. It has been well documented that polymorphic aggregates of Aβ can be produced by changes in the chemical environment and peptide preparations. As Aβ and several of its aggregated forms are known to interact directly with lipid membranes and this interaction may play a role in a variety of potential toxic mechanisms associated with AD, we determine how different Aβ(1-40) preparation protocols that lead to distinct polymorphic fibril aggregates influence the interaction of Aβ(1-40) with model lipid membranes. Using three distinct protocols for preparing Aβ(1-40), the aggregate species formed in the absence and presence of a lipid bilayer were investigated using a variety of scanning probe microscopy techniques. The three preparations of Aβ(1-40) promoted distinct oligomeric and fibrillar aggregates in the absence of bilayers that formed at different rates. Despite these differences in aggregation properties, all Aβ(1-40) preparations were able to disrupt supported total brain lipid extract (TBLE) bilayers, altering the bilayer's morphological and mechanical properties.

**2655-Pos Board B85**
**Thermodynamics of Abeta(16-21) Dissociation from an Amyloid Fibril**
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Here, we study the thermodynamic properties of $A\beta_{16-21}$ dissociation from an amyloid fibril using all-atom molecular dynamics simulations and TIP4P water. An umbrella sampling protocol is used to compute potentials of mean force (PMF) of peptide dissociation at five temperatures as well as changes in enthalpy, entropy and heat capacity upon dissociation. We find that similarly to protein unfolding, $A\beta_{16-21}$ dissociation is characterized by an unfavorable change in the enthalpy ($\Delta H>0$), a favorable entropic energy ($-T\Delta S<0$), and an increase in the heat capacity ($\Delta C_p>0$). The exposure of non-polar residues that are initially buried in the dry core of the fibril and become exposed to water as the peptide dissociates can be associated to the positive change in heat capacity. The increased freedom of the backbone and the loss of native contacts as the peptide dissociates from the fibril can explain the favorable entropy